Sarcoidosis of Beock

By THOMAS G. MILLIKEN, M.B., B.CH.

Institute of Pathology, Queen's University of Belfast

THE disease known as Boeck's sarcoidosis was first recognised in the form of skin lesion by Jonathan Hutchinson in 1869. In 1881 Ziegler described the lesion in lymph nodes as "large-celled indurative hyperplasia." Besnier in 1889 describe a skin manifestation and called it "lupus pernio." Further descriptions of sk lesions only were published by Tenneson (1892), Hutchinson again (1898), a Boeck (1899). Boeck noted enlargement of superficial lymph nodes, and followin clinical and histological studies of further cases (1905, 1916), came to the conclusio that it was a generalised disease which might affect lymph-nodes, mucou membranes, internal organs, and bones. As he had thought that the histologic changes in the skin resembled sarcoma, he had called the condition "multipl benign sarcoid of the skin," hence the name Boeck's sarcoidosis. He finall considered it to be an infectious process closely related to tuberculosis and possibl due to the tubercle bacillus. Schaumann was probably the first to describe it a a generalised disease in 1914, and in subsequent papers he called it "lympho granulomatosis benigna." Numerous accounts of cases have been given since especially on the Continent, and in America and England notably by Longcop and Pierson (1937), Snapper (1938), and Bodley Scott (1938).

Boeck's sarcoidosis is now recognised to be a generalised chronic disease o adult life affecting a multiplicity of tissues, but accompanied by relatively littl constitutional disturbance, with a relapsing course and a tendency to spontaneou remission. The lesions are characterised histologically by follicular mesenchyma hyperplasia. In the cases described in the literature, few organs have escaped the disease, but the lesions are most constant in lymphoid tissue, bone marrow skin, lungs, spleen, liver, eyes, and salivary glands, and at some time in the course of the disease there is a localised or generalised enlargement of lymph nodes. The histological appearance and to some extent the distribution of the lesions resemble those of tuberculosis, but there is no caseation, the tuberculin reaction is usually negative, and the tubercle bacillus has never been demonstrated. It has also been suggested that the condition is a reticulosis (Bodley Scott and Robb-Smith, 1936).

The tendency for the disease to involve the skin in different ways and to attac certain groups of tissues has given rise to a number of clinical pictures, which have acquired the names of their describers. The skin manifestations, which are present in about half the cases, are divided clinically into five types: Multiple benign nodular sarcoid of Boeck, benign miliary lupoid of Boeck, lupus pernio of Besnier, angio-lupoid of Brocq and Pautrier, and érythrodermie sarcoïdique of Schaumann. The bone lesions in the hands and feet, which produce typical punched-out shadows radiographically, are known as ostitis tuberculosa multiplex cystica of Jüngling, and the simultaneous involvement of the parotid gland and

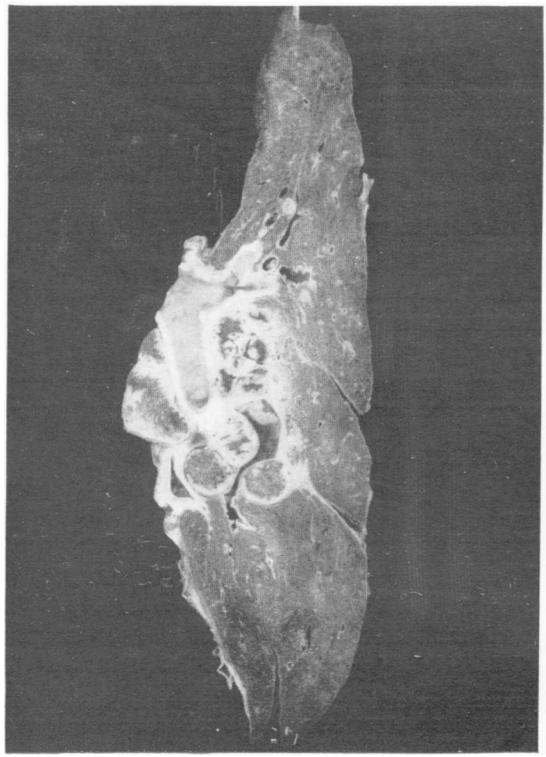

FIG. 1.

Section of right lung, x 2/3. Note collapse, enlarged bronchial lymph glands, distortion of lumen of pulmonary artery containing coiled thrombus, thrombi in smaller vessels, and very small white miliary nodules throughout lung, most numerous in the base.

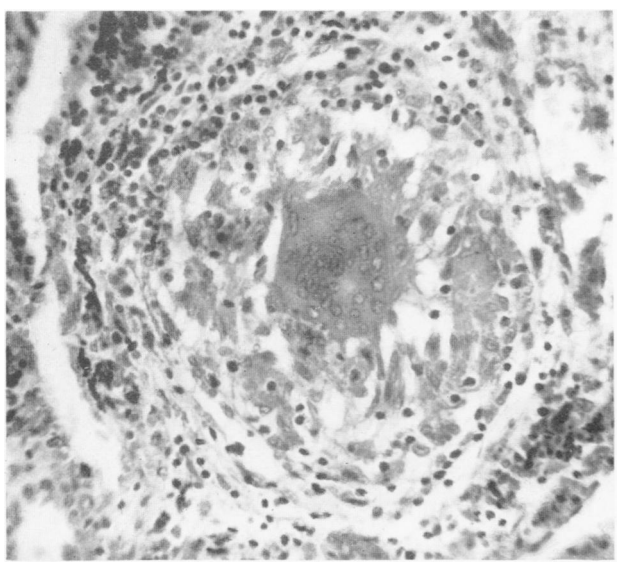

FIG. 2.

Sarcoid follicle in pulmonary lymph vessel. Note giant cell and epithelioid cells with branching cytoplasm, and zone of lymphocytes outside the endothelium of the vessel.

H. and E. x 280.

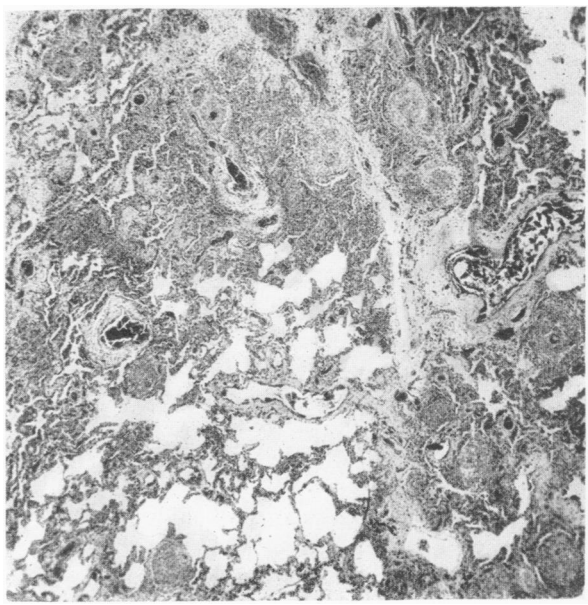

FIG. 3.

Low power view of lung to show thickened pleura (top left-hand corner) and aggregations of sarcoid follicles in subpleural and perivascular lymphatics. H. and E. x 20.

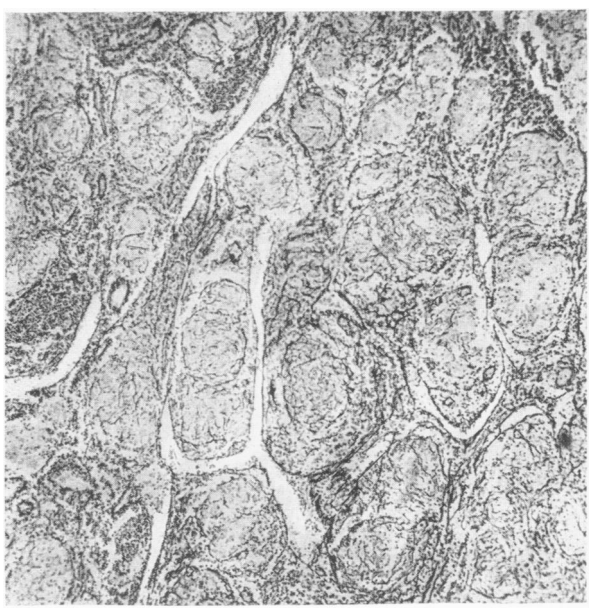

FIG. 4.

Foot's silver carbonate impregnation of lymph node, showing concentration of reticulin round the sarcoid follicles. x 60.

the uveal tract (iridocyclitis) is called uveoparotitis subchronica of Heerfordt. These conditions are different clinical expressions of the same pathological process.

A case has recently been reported in Ireland by Mitchell (1942). The diagnosis was made following biopsy from the skin and a lymph node, and was supported by negative tuberculin reactions and animal inoculation. The case was remarkable for the presence of lesions in the retina.

The following is an account of a case discovered at autopsy, in which the only lesions were in the lungs, bronchial lymph nodes, liver, and spleen.

Clinical History.

The patient was a stoutly built woman of 52 years, married, with two children. She was admitted to the Royal Victoria Hospital, Belfast, on 2nd April, 1941, complaining of severe pain in the right side of the chest. The pain came on suddenly, with shivering fits, and she had a slight cough with very little sputum. There had been a similar attack three weeks previously, and she gave a history of pleurisy nine years before. There was no family history of tuberculosis. She had been losing weight and was not sleeping well. Her menses had ceased six years before.

The pulse rate was 96 per minute, temperature 99.4°F., and respirations 28 per minute.

On examination, the only abnormal findings in the chest were fine crepitations on auscultation at both lung bases, especially posteriorly. Apart from tachycardia, there were no physical signs of disease in the heart, and examination of the alimentary, genito-urinary, and central nervous systems resulted in no abnormal findings.

A radiograph of the chest was reported as showing elevation of the right diaphragm and slight pleurisy in the right costo-phrenic angle, with congestion of the right base. Bacteriological examination of the sputum revealed Friedländer's bacillus, pneumococci, and micrococcus catarrhalis. No tubercle bacilli were found on direct examination or on culture. An electro-cardiogram showed tachycardia, flattening of T wave in lead ii, and inversion of T wave in lead iii—"Myocardial change." The urine was acid, of specific gravity 1020, and contained no albumen or sugar. A catheter specimen was sterile.

A diagnosis of broncho-pneumonia and pleurisy was made, and four grams of sulpha-pyridine administered daily. The temperature fell from 100.2°F. on the second day to normal in three days, but rose again to the previous level, and the drug was discontinued after six days. The pain and the pleurisy slowly disappeared, but the crepitations persisted, and the temperature fluctuated slowly between 99°F. and 101°F. The pulse rate remained fast, between 100 and 130 per minute, and was reduced by digitalis from an average of 116 to 80 per minute.

A further radiograph of the chest one week before death was reported as showing slight general enlargement of the heart of the aortic type. The pleurisy had disappeared, but the elevation of the right diaphragm persisted.

The patient was feeling very well until on the morning of 13th May, 1941, she sat up in bed after breakfast, collapsed suddenly, and died in a few seconds, six weeks after admission to hospital.

Autopsy.

The post-mortem examination was carried out three hours after death.

The body was that of an elderly female of stout build and good nutrition, a
was still warm. There was no jaundice, œdema, enlargement of superfi
lymph nodes, nor disease of the skin.

The pericardial sac contained a small amount of clear yellow fluid. The l
pleural cavity was entirely obliterated by fibrous adhesions. The right pleu
sac was bridged by three or four fleshy adhesions over the lower lobe, the b
was adherent to the diaphragm, and the lung considerably collapsed. There w
no excess of fluid. The abdominal cavity contained neither free fluid nor g
and the organs occupied normal positions.

The neck organs, heart, and lungs were removed en bloc, and on sectioni
the hilum of the right lung, the right pulmonary artery was seen to contain a ma
of coiled thrombus. This thrombus also filled the main pulmonary artery and t
left branch, and extended through the pulmonary valve into the right ventricl
The embolus when uncoiled was about eight inches long and much branched, a
the main stem at its widest was one centimetre in diameter.

The femoral, internal and external and common iliac veins were examined f
the presence of thrombus, but none was found. The circumference of the low
limbs was measured at different levels from the ankle to the thigh, and was fou
to be everywhere equal on both sides. The source of the embolus was n
discovered.

The heart weighed 11 ounces. There was no thrombus in the auricul
appendages. The endocardium and valves were normal. The right ventricle w
hypertrophied, the wall being one centimetre in thickness. The myocardium w
brownish-red in colour and appeared healthy throughout.

The right lung was small and collapsed (see fig. 1). The pleura was smoot
greyish-purple in colour, and semi-opaque, and over the lower lobe was mu
thickened by the attachment of several fleshy fibrous bands. Widely scatter
beneath the pleura were many small greyish-white nodules averaging one mil
metre in diameter. They felt slightly firmer in consistency than the surroundi
lung tissue. In the upper lobe, near the apex posteriorly, there was a firm reddis
purple area about four centimetres by three, which was raised above t
surrounding lung and well demarcated, having the gross appearance of an infar
The overlying pleura was dull and slightly thickened.

The hilum lymph nodes were greatly enlarged, discrete, and of the consisten
of firm rubber. A number were normal in size and consistency. The bronch
mucosa was pink, moist, and rugose. The main branches of the pulmonary arte
contained pale ante-mortem blood clot. The enlarged lymph nodes, on sectio
were firm and markedly anthracotic, the central parts being black or greyis
black in colour, surrounded by a fairly regular outer rim of greyish-white tissu
about three millimetres wide.

The cut surface of the lung was brownish-red in colour, and scattered throughou
were many small grey, almost bluish-white, nodules one or two millimetres i

iameter, similar to those seen beneath the pleura. Many of the smaller blood-essels contained firm blood clot.

The left lung.—The bronchial lymph nodes, blood-vessels, and alveolar tissue ere similar in appearance to the right, except that there was no infarct, the arietal and visceral layers of pleura were closely adherent, and there was less llapse.

The liver was enlarged and weighed four and a half pounds. The capsule was mooth, and, on section, brown liver cells could be seen against a pale yellowish-rown background. The organ was soft and friable. No nodules similar to those the lung were detected. The gall-bladder and portal vein were normal.

The spleen weighed five ounces and was not enlarged. The capsule was smooth, nd just beneath it, at the lower pole, there was a small greyish-white nodule ne millimetre in diameter, similar to the sub-pleural nodules seen in the lung. o similar lesions could be detected on the cut surface, which was dark red in olour. The pulp was very soft and the capsule did not retract from the cut edge. he Malpighian bodies and trabeculæ were clearly visible.

The alimentary and genito-urinary tracts revealed no abnormality, and no lesions ere found in the thyroid, parathyroids, adrenals, nor pancreas. There was slight heromatous change in the intima of the aorta. The brain and bones were not amined.

Microscopical Examination.

Only the essential pathological lesions are described.

Lungs.—Scattered throughout the alveolar tissue of both lungs were numerous rcular or oval cellular follicles. Their structure was everywhere similar. They ere composed of large pale epithelioid mononuclear cells with slightly eosino-ilic cytoplasm and large clear nuclei, which contained one or two tiny chromatin odes. The nuclei were round, oval, or slightly irregular in shape. In most of e follicles there were one or more multinucleate giant cells of the Langhans pe containing any number of nuclei up to fifty. As many as ten giant cells were en in one follicle. Their cytoplasm was often branched, extending radially tween the nuclei of the epithelioid cells, whose cytoplasm was also frequently anched, so that among the cells of the follicle there were irregular clear spaces ross which stretched thin pink-staining cytoplasmic bridges (see fig. 2). Some the follicles contained a few lymphocytes and eosinophils. Nearly all of the llicles were inside lymphatic vessels, being enclosed by at least one layer of ttened endothelial cells, which in turn were surrounded by lymphocytes. The ra-lymphatic situation of the follicles was apparent also from their distribution. ey were most concentrated just beneath the pleura in the sub-pleural lymphatic xus, and in the depths of the lungs were always in a perivascular or peribronchial mph channel (see fig. 3). Some were in the walls of bronchioles, splitting up the scle-coats beneath intact mucous membrane.

The pleura overlying areas in which the follicles were present, was thickened fibrous tissue containing dilated and engorged capillaries. Beneath the adhesions the right lower lobe the follicles were particularly numerous and infiltrated tensively by lymphocytes. The adhesions consisted of bands of fibrillar fibrous

tissue containing capillaries and a few lymphocytes, such as might be forme
the organisation of a fibrinous exudate. There was nothing in their histolo
appearance to suggest a specific ætiology apart from the sub-pleural concentr
of follicles.

A section of the hæmorrhagic infarct at the periphery of the lung showed
it was of some standing, and its central portion had undergone necrosis.
overlying pleura was much thickened by fibrous tissue in which there were di
and engorged capillaries, many small hæmorrhages, and scattered foci of l
pale mononuclear cells and lymphocytes. The sub-pleural lymphatics were di
and their endothelium swollen. They contained large mononuclear cells
ingested red blood-corpuscles and carbon particles.

A smaller hæmorrhagic infarct deep in the lung was completely walled o
cellular fibrous tissue infiltrated with large mononuclear cells and lymphoc
and containing epithelioid follicles. At its edges organisation of the infarct
ingrowing capillaries and fibroblasts had begun. In the same section there
a small artery containing an organised thrombus. Throughout the remainde
both lungs there were many small and occasional large vessels containing thro
in various stages of organisation.

In sections from the bases of the lungs the alveoli contained much œdema fl

Bronchial lymph nodes.—Some of these were not enlarged and presented nor
architecture. In the enlarged nodes the lymphoid tissue was almost c
pletely replaced by follicular collections of cells similar to those seen in
lung. There were fewer giant cells and more lymphocytes than in the lung lesi
There was no necrosis nor caseation. Where the enlarged glands pressed u
the pulmonary artery there was considerable thinning of the media, and Ha
elastin stain revealed that the elastic tissue at this point was reduced to a qua
of its width in the rest of the vessel.

Liver.—The liver cells had undergone extensive fatty degeneration which
mainly periportal in distribution. There were several follicles or small group
follicles composed of epithelioid cells with giant cells, similar to those in the l
and lymph nodes. The follicles had no predilection for any one part of the lob
being present in all parts. In two of the larger groups there were small area
pink-staining necrotic material. In these liver lesions there was a relatively la
number of eosinophil polymorphonuclear leucocytes, with a few lymphocytes
the periphery of the follicles.

Spleen.—The red pulp was very congested. The Malpighian bodies were diff
and composed in their peripheral parts largely of plasma cells. Plasma cells
surrounded many trabeculæ, indicating a reaction to infection. There w
several epithelioid follicles in the spleen similar to those in the lung,
there was nothing remarkable about their distribution in relation to spl
architecture.

No other organs on microscopic examination showed lesions of any kind.

The resemblance of the lesions described to tuberculous follicles was immediat
apparent, but nowhere was there any evidence of caseation, and only two ve

mall areas of necrosis were seen in the liver lesions. Staining by Ziehl-Neelsen's ethod of numerous sections of lung, lymph nodes, liver, and spleen failed to veal any acid-fast bacilli. Van Gieson's stain and Masson's trichrome stain owed that each mesenchymal follicle was partly surrounded by a few thin llagen fibrils such as would normally be present in any tissue, and there was evidence of a fibroblastic reaction as in miliary tubercles. Impregnation by ot's silver carbonate (fig. 4) demonstrated that each follicle was almost enclosed strands of reticulin, with many fine branching inter-cellular fibrils in the centre.

Anatomical Diagnosis.

Chronic pulmonary embolism; collapse and infarction of right lung; final fatal embolus:

Boeck's sarcoidosis of bronchial lymph nodes; miliary sarcoidosis lungs, liver, and spleen:

Hypertrophy of right ventricle:

Atheroma of aorta.

Discussion.

The diagnosis of Boeck's sarcoidosis on histological appearance, even without gative tuberculin reactions and animal inoculations, seems justified, and is pported by the absence of demonstrable acid-fast bacilli. The distinction from engel-Wolbach sclerosis or giant-cell histiocytic sinus reticulosis (Robb-Smith) in the absence of fibrosis; also, in the sarcoid the greatest concentration of iculin is at the periphery, whereas in Stengel-Wolbach's sclerosis it is among cells in the centre of the follicle. The presence of extensive lung lesions also cludes the reticulosis.

t is generally accepted that the lesions of Boeck's sarcoid are clinically benign, d seldom, if ever, cause the death of the patient. There is no reason to believe t the present case departs from this dictum. The attack of pleurisy nine years ore death was probably on the left side, where the pleural cavity was obliterated firm adhesions. Nothing remains to show its ætiology. The cause of the two cks, nine and six weeks before death, was undoubtedly pulmonary infarction, onic embolism, perhaps with the help of the sarcoid lesions, having produced pre-requisite venous congestion. The patient was brought to bed by the last ck of pleurisy, and the decubitus resulted in stasis. This was a factor in sing the thrombosis, from which the final fatal embolus was set free.

here is no evidence that the sarcoid lesions alone could have produced the risy. The age of the sarcoids is difficult to judge. It is said that they ogress slowly, retaining their cellularity for several months before undergoing us replacement. The lesions in this case were cellular, and none showed any ence of fibrosis. It cannot be assumed, however, that even at their inception he presence of a possible inflammatory agent, they could have caused a pleural date.

he radiographs of the lungs in this case showed features which have been tantly described in pulmonary sarcoidosis. The hilum shadows were prominent, ading towards the bases; linear shadows in the lung fields presented a slightly ulate appearance, sometimes called "marbleisation," and there were many

small circular shadows three to five millimetres in diameter, especially in the l which resembled those of miliary tuberculosis. There is a definite pathol basis for each of these appearances in the enlargement of hilum glands an presence of perivascular and peribronchial sarcoids in linear and circular gr Slight cough as the only symptom, and limitation of physical signs to l crepitations, are also constant findings.

As regards the ætiology of sarcoidosis, no deductions can be drawn from case, and general impressions are vitiated by the co-existence of the em phenomena. The prevailing view is that the disease is a peculiar form of be tuberculosis, caused by a filterable form of the bacillus or by the products o growth. The absence of caseation and of skin sensitivity is explained by theory of anergy. In the present case the scattered miliary sarcoids in the l and spleen appear to be blood-borne, and the fatty degeneration of the completes a likeness to miliary tuberculosis. Some of the cases reported as he or chronic miliary tuberculosis may be pulmonary sarcoidosis (Bödeker, 193

Another suggestion is that it is a systematised disease of the reticulo-endoth system (a reticulosis), comparable to Hodgkin's disease, and likewise of unkn ætiology. The resemblance of the sarcoid lesions to those of "chronic prolifera tuberculosis," Crohn's disease (regional ileitis), tuberculoid leprosy, Leishmani of the skin, and to lesions produced by injections of paraffin, oils, fats, an phosphatide fraction of the lipoids of the tubercle bacillus, suggest that sarcoid may be a non-specific tissue response to a variety of pathogenic agents. It difficult, however, to accept a non-specific ætiology for such a characteristic well-defined pathological process.

Summary.

(1) An account is given of a case of Boeck's sarcoidosis discovered at auto in a patient dying of pulmonary embolism. The lesions were in the lungs, bronch lymph nodes, liver, and spleen.

(2) The literature, the pathological histology, the radiographic findings in lungs, the biological effects of sarcoidosis, and the ætiology of the condition briefly discussed.

References.

Besnier, E.: *Ann. de dermat. et syph.*, 1889, 10, 333.
Bödeker, F.: *Med. Klin.*, 1932, 28, 929.
Boeck, C.: *Jour. Cut. and Genito-Urinary Dis.*, 1899, 17, 543.
Boeck, C.: *Arch. für Dermat. u. Syph.*, 1905, 73, 71, and 301.
Boeck, C.: *Ibid.*, 1916, 121, 707.
Hutchinson, J.: *Arch. Surg.*, 1889, 9, 307.
Longcope, W. T., and Pierson, J. W.: *Bull. Johns Hopkins Hospital*, 1937, 60, 223.
Mitchell, D.: *Irish Jour. Med. Sc.*, 1942, 6th Series, No. 198, 204.
Schaumann, J.: *Brit. Jour. Dermat. and Syph.*, 1924, 36, 515.
Schaumann, J.: *Ibid.*, 1936, 48, 399.
Robb-Smith, A. H. T.: *Jour. Path. and Bact.*, 1938, 48, 457.
Scott, R. B., and Robb-Smith, A. H. T.: *St. Bart.'s Hosp. Rep.*, 1936, 69, 143.
Scott, R. B.: *Brit. Med. Jour.*, 1938, 2, 777.
Tenneson, M.: *Bull d. l. Soc. franç. d. dermat. et d. syph.*, 1892, 3, 417.